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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/504,280 | 02/15/2000 | Mike A. Clark | phoe-0057 | 5368 |

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11/04/2002

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EXAMINER

ROMEO, DAVID S

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 11/04/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/504,280

Applicant(s)

CLARK, MIKE A.

Examiner

David S Romeo

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 August 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 9-13 and 18-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 and 14-17²⁴ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-24 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment filed August 21, 2002 (Paper No. 12) has been entered. Claims 1-23 are pending. Claims 9-13, 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to, or to the extent that they are drawn to, a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. Claims 1-8, 14-17, 24 are being examined to the extent that they read upon an elected invention and/or species. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Maintained Formal Matters, Objections, and/or Rejections:***Claim Rejections - 35 USC § 102***

Claims 1-7, 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsutsumi (AL, cited by Applicants).

The rejection of record is applied to claim 24 for reasons of record. See the last Office action at page 4, lines 2-5.

Applicants argue that Tsutsumi fails to teach each limitation of the claims because Tsutsumi's PEG-5000 is not in the molecular weight range recited in the claims, Applicants did not consider PEG with a MW of 5000 to fall within the range of about 10000 to about 20000,

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and Applicants request that the examiner provide an affidavit. Applicants arguments have been fully considered but they are not persuasive. There is nothing in the specification or the prior art to provide any indication as to what range of molecular weight is covered by or excluded from the terms “about”, “bordering on the ridiculous”, or “reasonably close to.”

5 Applicants argue that Tsutsumi fails to teach each limitation of the claims because Tsutsumi fails to teach that the TNF is covalently bound to between about five and twelve molecules. Applicants arguments have been fully considered but they are not persuasive. Tsutsumi teaches 100, 71, 56, and 29% degrees of PEG-modification of TNF- α (Table I). Human TNF- α has eight lysine residues, according to Figure 3 of the present application. A 100,
10 71, 56, or 29% degree of PEG-modification of TNF- α corresponds to modifying said TNF by covalently bonding to it between about five and twelve PEG molecules.

Claim Rejections - 35 USC § 103

Claims 1, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsutsumi
15 (AL, cited by Applicants) and Nakamura (u10).

Applicants argue that Tsutsumi fails to teach each limitation of the claims because Tsutsumi's PEG-5000 is not in the molecular weight range recited in the claims, Applicants did not consider PEG with a MW of 5000 to fall within the range of about 10000 to about 20000, and Applicants request that the examiner provide an affidavit. Applicants arguments have been
20 fully considered but they are not persuasive. There is nothing in the specification or the prior art to provide any indication as to what range of molecular weight is covered by or excluded from the terms “about”, “bordering on the ridiculous”, or “reasonably close to.”

Applicants argue that Tsutsumi fails to teach each limitation of the claims because Tsutsumi fails to teach that the TNF is covalently bound to between about five and twelve molecules. Applicants arguments have been fully considered but they are not persuasive. Tsutsumi teaches 100, 71, 56, and 29% degrees of PEG-modification of TNF- α (Table I).

5 Human TNF- α has eight lysine residues, according to Figure 3 of the present application. A 100, 71, 56, or 29% degree of PEG-modification of TNF- α corresponds to modifying said TNF by covalently bonding to it between about five and twelve PEG molecules.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on
10 combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that Nakamura fails to suggested the TNF recited in claim 8 because Nakamura's TNF has amino acid residues 1-7 deleted and amino acid residues 8-10 substituted, whereas the claimed TNF is mutated by deleting amino acid residues 1-9. Applicants arguments
15 have been fully considered but they are not persuasive. Claim 8 recites "TNF mutated by deleting amino acids 1-9 of the mature TNF protein." Nakamura's TNF wherein amino acid residues 1-7 are deleted and amino acid residues 8-10 are substituted is TNF mutated by deleting amino acids 1-9 of the mature TNF protein", as recited in claim 8.

Applicants argue that the Office has failed to provide motivation to combine the
20 references. Applicants arguments have been fully considered but they are not persuasive. One of ordinary skill in the art would be motivated to combine these teachings because one of ordinary skill in the art would be motivated to combine the enhanced circulating half life and

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tumoricidal activity of the pegylated TNF taught by Tsutsumi with the higher anti-tumor activity, higher binding activity to TNF receptors, the possible cachectin activity the same as that of wild-type TNF, and the lower acute lethal toxicity of mutant 471 taught by Nakamura in order to obtain a more promising anti-cancer agent.

5 In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the
10 applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No claims are allowable. Limiting the claims to PEG molecules having a weight average
15 molecular weight in the range of at least 10000 to about 40000 would obviate the rejection under 35 U.S.C. 102(b) as being anticipated by Tsutsumi (AL, cited by Applicants).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

20 A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306

AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 3, 2002